line 30, and page 20, line 3 of the specification. Applicants believe that Examiner's objections are now obviated in view of the present amendment to the brief description of the Figure 5.

Claims

Claim 1 is amended to eliminate the "comprising" language in the preamble to better clarify the subject matter of the claim sought.

Claim 1 is further amended for clarity to refer to "a nucleic acid molecule which hybridizes" instead of "nucleic acid molecules which hybridize" in clause (a).

Claim 1 is further amended for clarity to recite "the nucleic acid of SEQ ID NO:1" instead of "a nucleic acid of SEQ ID NO:1" in line 3 of claim 1.

Claim 1 is further amended to substitute the phrase "Lens Epithelial Cell Derived Growth Factor polypeptide" for the phrase "polypeptide that induces protein synthesis in an epithelial cell."

Claim 1 is further amended to eliminate subject matter in clause (b) of claim 1 as originally filed, relating to "deletions, additions and substitutions of a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1 which codes for a Lens Epithelial Cell Derived Growth Factor polypeptide, and which code for a respective Lens Epithelial Cell Derived Growth Factor polypeptide."

Claim 3 is amended to eliminate the "fragment thereof" language.

Claim 26 is amended for clarity to further define an agent that selectively binds to the isolated nucleic acid of claim 1, as a *nucleic acid or polypeptide* agent.

Claim 26 is further amended in accordance with Applicants' election under the restriction requirement, and is now directed only to nucleic acids of claim 1 and not to expression products thereof (i.e., polypeptides).

Rejection of Claims Under 35 U.S.C. §112, first paragraph

Claims 1, 8, 10 and 26 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors, as the time the application was filed, had possession of the claimed invention.

According to the Examiner, "with the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and therefore conception is [not] achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

method of isolation," and that "adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it."

The Examiner further states that "the nucleic acid itself is required," according to "Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co., Ltd., 18 USPQ2d 1016." Respectfully, Applicants disagree.

The Examiner raises the issue that the claims to LEDGF nucleic acids, as previously constituted, fall under the holding of Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) (hereinafter "*Amgen*"). Applicants suggest that this issue is moot given the amendments to the claims. Specifically, in *Amgen*, the court held that conception of a chemical compound such as a nucleic acid requires that the inventor be able to define the compound (e.g., describe its structure) so as to distinguish it from other compounds, and to describe how to obtain it, rather than simply defining it solely by its principal biological property/activity. The claims at issue in *Amgen* were not limited by sequence, but rather sought to cover all nucleic acids having a particular function (e.g., erythropoietin [EPO] activity) without reciting the structure of an EPO nucleic acid. In contrast, the amended claims in the instant application recite that the claimed nucleic acids hybridize to SEQ ID NO:1 and have LEDGF activity, and Applicants have taught how to isolate such nucleic acids by hybridization and determination of the activity of the encoded protein. Thus, *Amgen* is not applicable to the amended claims.

The Examiner further argues that "[o]ne cannot describe what one has not achieved," according to "Fiddes v. Baird, 30 USPQ2d 1481, 1483" (hereinafter "*Fiddes*"). According to the Examiner, "in Fiddes v. Baird, claims directed to mammalian FGFs were found unpatentable due to lack of written description for the broad class," and that "the specification provided only the bovine sequence." Respectfully, Applicants disagree.

The subject matter at issue in *Fiddes* relates to Count 2 of the interference in which Fiddes and Baird were involved. Count 2 was defined by the administrative judge as "a recombinant DNA molecule consisting essentially of a DNA sequence encoding mammalian basic fibroblast growth factor." The specification of U.S. Patent No. 4,956,455, issued to Baird *et al.*, set forth the 146 amino acid sequence for bovine pituitary FGF and only a theoretical DNA sequence which could encode bovine pituitary FGF. Based on the specification of the '455 patent the court stated that the '455 patent did not contain a written description for the broad class of mammalian FGFs as exemplified in the interference count. The court further stated that the patent did not teach the naturally occurring gene encoding the factor and thus the Applicant was not in possession of the naturally occurring gene encoding bovine pituitary FGF. In

contrast, the amended claims in the instant application recite that the claimed nucleic acids hybridize to SEQ ID NO:1 (the naturally occurring LEDGF cDNA) and have LEDGF activity, and Applicants have taught how to isolate such nucleic acids by hybridization and determination of the activity of the encoded protein. Thus, *Fiddes* is not applicable to the amended claims.

The Examiner further argues that "whereas the instant specification provides a detailed description of a particular DNA molecule, SEQ ID NO:1, encoding a particular protein, SEQ ID NO:2, the instant specification does not provide a structural formula which is definitive of all hybridizing DNA molecules and mutated variants thereof that encode a LEDGF protein with the desired activity." The Examiner further states that "only SEQ ID NO:1 but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph." Respectfully, Applicants disagree.

The controlling case law for an adequate written description of a nucleic acid molecule is the case of the University of California v. Eli Lilly and Company, and cases cited therein. University of California v. Eli Lilly and Co., 43 USPQ 2d 1398 (Fed. Cir. 1997) (hereinafter "*Lilly*").

In the *Lilly* case, the court held that a generic statement referring to a nucleic acid molecule such as "vertebrate insulin cDNA" was not an adequate written description of the nucleic acid molecule because it did not distinguish the claimed molecule from others in the genus of like molecules except by its functional aspects. *Id.* at 1406. The problem with the written description of an insulin cDNA in the University of California application was that it "does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." *Id.* The court further stated that a proper written description "of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under §112, paragraph 1, by showing the enablement of a representative number of species within the genus." *Id.*

Therefore, the court in *Lilly* decided that a description of a genus of nucleic acid molecules which was only functional was not an adequate written description of that set of nucleic acid molecules. That problem is plainly not shared by the disclosure of Applicants in the instant application. The question which must be asked is whether there is an adequate written description of a nucleic acid molecule under the present case law, which "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *Id.* at 1404, citing *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993).

Claim 1 as amended herewith no longer contains language directed to "deletions, additions and substitutions of a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1 and which codes for a Lens Epithelial Cell Derived Growth Factor polypeptide, and which code for a respective Lens Epithelial Cell Derived Growth Factor polypeptide." (former clause *(b)* of Claim 1). Applicants have provided both structure and physical properties of the claimed nucleic acid molecules, and therefore Applicants assert that they have provided an adequate written description which would allow one skilled in the art to "visualize or recognize the identity of the members of the genus." *Lilly*, 43 USPQ 2d at 1406.

Claims 1, 3, 8, 10 and 26 stand rejected under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and/or use the invention commensurate in scope with these claims. According to the Examiner, "the specification, while being enabling for a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, does not reasonably provide enablement for nucleic acid molecules which hybridize to SEQ ID NO:1 and encode a lens epithelial cell derived growth factor polypeptide, or for a nucleic acid molecule comprising deletions, additions and substitutions of nucleic acid molecules which hybridize to SEQ ID NO:1 and encode a respective lens epithelial cell derived growth factor polypeptide, or for a fragment of SEQ ID NO:13 without regard to the structure and/or function thereof, or for an agent that binds a nucleic acid molecule."

According to the Examiner, "the current claim limitations are analogous to those of claim 7 of U.S. Patent No. 4,703,008, which [was] held to be invalid under 35 U.S.C. §112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ 2d 1016 (CAFC, 3/5/91, see page 1026, section D)." The Examiner states that "in that instance a claim to nucleic acid molecule encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. §112, first paragraph, for want of enablement." Respectfully, Applicants strongly disagree with the Examiner's interpretation of the *Amgen* court's holding.

The claim at issue, Claim 7 of U.S. Patent No. 4,703,008, is recited herein for Examiner's convenience:

> *7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.*

As noted by the court "Claim 7 is a generic claim, covering all possible DNA sequences that will encode any polypeptide having an amino acid sequence 'sufficiently duplicative' of EPO to possess the property of increasing production of red blood cells." Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991) (see 2nd full paragraph of section D). As the Examiner can appreciate, there is no reference to a single nucleotide sequence in claim 7.

Applicants would like to reiterate the arguments presented earlier relating to this exact issue concerning claim 7. In *Amgen*, the court held that conception of a chemical compound such as a nucleic acid requires that the inventor be able to define the compound (e.g., describe its structure) so as to distinguish it from other compounds, and to describe how to obtain it, rather than simply defining it solely by its principal biological property/activity. Claim 7, as the court noted, is not limited by sequence, and Amgen used language sought to cover all nucleic acids having a particular function (e.g., EPO activity) without reciting the structure of an EPO nucleic acid. In contrast, the amended claims in the instant application recite that the claimed nucleic acids hybridize to SEQ ID NO:1 and have LEDGF activity, and Applicants have taught how to isolate such nucleic acids by hybridization and determination of the activity of the encoded protein. Thus, *Amgen* is not applicable to the amended claims.

The Examiner argues that "there are no limitations to the 'fragment' of claim 3."

Claim 3 as amended herein no longer recites "or a fragment thereof," thus rendering the rejection of claim 3 under 35 U.S.C. §112, first paragraph, moot.

The Examiner further argues that "the limitation 'agent' (claim 26) is analogous to a single means claim of the type disparaged by the court."

Claim 26 as amended is now directed to a nucleic acid or polypeptide agent that selectively binds to the isolated nucleic acid of claim 1, thus rendering the Examiner's rejection of claim 26 under 35 U.S.C. §112, first paragraph, moot.

Claims 4-7, 9 and 11 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that "the claim [4] is drawn to a fragment of SEQ ID NO:1 that is unique within the

human genome," and argues that "in order to make such a fragment knowledge of the sequences of the genomes of all humans." Respectfully, Applicants disagree.

Claim 4 as amended herein is directed to "a fragment of a nucleic acid molecule of SEQ ID NO:1, of sufficient length to represent a sequence identifying a nucleic acid encoding a polypeptide that induces protein synthesis in an epithelial cell." Applicants have eliminated the language "unique within the human genome," from claim 4 as originally filed. A fragment of a nucleic acid molecule of SEQ ID NO:1, as claimed in amended claim 4 of the instant application, refers to a fragment that can be characterized by one of ordinary skill in the art as one identifying a nucleic acid encoding a polypeptide that induces protein synthesis in an epithelial cell (e.g., a nucleic acid molecule of SEQ ID NO:1). Such fragment will, for example, hybridize under stringent conditions to a LEDGF nucleic acid molecule. Such fragment will, if of sufficient length, encode a polypeptide that induces protein synthesis in an epithelial cell as taught by Applicants in the instant specification (see at least page 9, lines 3 and 4). Those skilled in the art are well versed in methods for selecting such sequences, typically by performing homology searches using an algorithm such as NCBI's BLAST, although, in addition, they may also perform *in vitro* confirmatory hybridization and sequencing analysis.

Rejection of Claims Under 35 U.S.C. §112 (second paragraph)

Claims 1, 8, 10 and 26 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention.

According to the Examiner, claims 1, 8, 10 and 26 are indefinite over the recitation of "comprising (a) nucleic acid molecules which hybridize" because it is unclear if the claimed nucleic acid molecule is a chimera comprising the entire universe of hybridizing nucleic acid molecules or if it comprises a single nucleic acid molecule within such a universe."

Claim 1 as amended herein no longer recites the word "comprising" in the preamble. It has been replaced with the phrase "selected from the group consisting of." Applicants believe that claim 1 as amended now conveys more precisely the metes and bounds of Applicants' invention, thus rendering the indefiniteness rejection moot.

According to the Examiner, claims 1, 8, 10 and 26 are indefinite over the recitation of "stringent conditions," because "stringency varies according to the hybridization conditions and the particular hybrid under study." Applicants, respectfully disagree.

The term "stringent conditions" is defined in the specification (see page 11, line 29 - page 12, line 3). For Examiner's convenience, these "stringent conditions" are presented below:

> "More specifically, stringent conditions, as used herein, refers, for example, to hybridization at 65°C in hybridization buffer (3.5 x SSC, 0.02% Ficoll, 0.02% polyvinyl pyrolidone, 0.02% Bovine Serum Albumin, 2.5mM NaH_2PO_4(pH7), 0.5% SDS, 2mM EDTA). SSC is 0.15M sodium chloride/0.15M sodium citrate, pH7; SDS is sodium dodecyl sulphate; and EDTA is ethylenediaminetetracetic acid. After hybridization, the membrane upon which the DNA is transferred is washed at 2 x SSC at room temperature and then at 0.1 x SSC/0.1 x SDS at temperatures up to 68°C."

One of ordinary skill in the art will be familiar with other conditions, reagents, and so forth which can be used, and would result in a similar degree of stringency, without having to perform undue experimentation to obtain such conditions. One of ordinary skill in the art will be able to manipulate the conditions in a manner to permit, for example, the clear identification of homologs and alleles of LEDGF nucleic acids of the invention. Stringent conditions used in the hybridization of nucleic acids are well in the art.

According to the Examiner, claims 1, 8, 10 and 26 are indefinite over the recitation of "a nucleic acid of SEQ ID NO:1" (claim 1, line 3) because it is unclear if the nucleic acid of SEQ ID NO:1 or some portion thereof is intended."

Claim 1 as amended herein no longer recites "a nucleic acid of SEQ ID NO:1" in line 3 of claim 1, thus rendering the indefiniteness rejection moot.

According to the Examiner, claims 1, 4-11 and 26 are indefinite because they recite the terms "lens epithelial cell derived growth factor polypeptide" or "respective lens epithelial cell derived growth factor polypeptide." According to the Examiner, "the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of 'lens epithelial cell derived growth factor polypeptide' [so that] an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term." Applicants, respectfully disagree.

Independent claims 1 and 4, as amended, now recite a nucleic acid encoding "a polypeptide that induces protein synthesis in an epithelial cell." Support for this amendment can be found throughout the specification, and at least on page 3, lines 7-14, and on page 10 lines 3-4. Applicants have taught throughout the specification of a lens epithelial cell derived growth factor polypeptide and the properties

of such polypeptide (i.e., its ability to induce protein synthesis in an epithelial cell, and/or to stimulate growth.

In addition, Applicants have taught of assays on detecting such LEDGF activity throughout the instant application (see at least Examples 6, 7, 8 and 9, of the specification). Applicants, thus, believe that such language is not indefinite, and that one of ordinary skill in the art would be aware of the metes and bounds of the invention.

According to the Examiner, claims 4-7, 9 and 11 are indefinite over the recitation of "represent a sequence unique within the human genome" because it is unclear which properties of the claimed nucleic acid molecule are supposed to be unique and which are not."

Claim 4 as amended herewith no longer recites "unique within the human genome," thus rendering the foregoing indefiniteness rejection moot.

According to the Examiner, claims 4-7, 9 and 11 are indefinite over "the recitation of 'identifying a nucleic acid molecule encoding a LEDGF' because the nature and extent of the 'identification' are unclear, [for example] "it is unclear if the 'identification' is by virtue of hybridization or an encoded polypeptide or a functional activity thereof." Applicants respectfully disagree.

Applicants throughout the instant specification teach about the structure of LEDGF nucleic acids, encoded polypeptides, functional activity of the foregoing molecules as well as mehtods for identifying such molecules including hybridization. One of ordinary skill in the art will be able to identify such LEDGF molecules based on one or more LEDGF properties as taught by Applicants in the instant specification.

According to the Examiner, claim 26 is indefinite over the "recitation of 'control' because the claim does not set forth the material element or combination of elements which is unique to, and, therefore, definitive of a 'control,' [so that] an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term." Applicants respectfully disagree.

One of ordinary skill in the art is well aware of what the term 'control' implies. In addition, Applicants throughout the instant specification teach about 'controls' that could be used, at least, in conjunction with the kits of the instant invention. For the Examiner's convenience the following example of the teaching of a 'control' that appears in page 28, lines 19-24 of the specification, is recited below:

> "The preferred kits would include controls such as known amounts of nucleic acid probes, LEDGF epitopes (such as LEDGF expression products) or anti-LEDGF antibodies, as well as instructions or other printed material. In certain embodiments the printed material can characterize risk of developing a cataract based upon the outcome of the assay. Additionally, anti-β-crystallin antibodies and β-crystallin epitopes can also be included for control purposes."

One of ordinary skill in the art will be able, without undue experimentation, to easily determine and select an appropriate control to use in an assay. A 'control' in a LEDGF nucleic acid expression assay, for example, could be an appropriate tissue sample from an apparently healthy subject. LEDGF nucleic acid expression in such sample could therefore be used as a 'control' when LEDGF nucleic acid expression in a similar tissue sample from a subject suffering from cataracts (a diseased subject), is obtained. Other controls could be utilized based upon the assay being performed, and the skilled artisan could easily choose a control to fit the intended purpose of the assay without undue experimentation.

In view of the foregoing amendments and arguments, Applicants believe that the foregoing rejections of claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

Rejection of Claims Under 35 U.S.C. §102

Claims 1, 8, 10 and 26 stand rejected under 35 U.S.C. §102(e) as being anticipated by Fiddes, et al. (A_{10}).

According to the Examiner, "Fiddes, et al. teach an isolated nucleic acid molecule encoding bFGF (col. 4, lines 38-41), an expression vector comprising the nucleic acid molecule operably linked to a promoter, and a host cell transformed with the expression vector (col. 11, line 6, through col. 14, line 55; col. 19, line 10, through column 25, line 33)." The Examiner further argues that "the isolated nucleic acid molecule [of Fiddes et al.] comprises deletion, additions and substitutions of nucleic acid molecules which hybridize to SEQ ID NO:1 and it encodes a respective lens epithelial cell derived growth factor polypeptide."

Claim 1 as amended herein no longer recites "deletions, additions and substitutions of a nucleic acid molecule which hybridizes under stringent conditions to a molecule consisting of a nucleic acid of SEQ ID NO:1," thus rendering the rejection moot.

Applicants believe that the LEDGF molecules claimed in amended claim 1 will not hybridize to the bFGF nucleic acid of Fiddes et al., when the limitations of amended claim 1 are taken into consideration (e.g., with regard to stringency). Applicants, therefore, respectfully request withdrawal of the rejection of the foregoing claims under 35 U.S.C. §102(e).

New Objection-Specification

The Examiner objects Applicants' "attempt to incorporate subject matter into this application by reference to GenBank accession numbers (Table III) as improper because the nucleotide sequences are critical or essential material to the practice of the invention."

Applicants are filing concurrently herewith each of the GenBank sequences described in Table III as part of a PTO-1449 and an Information Disclosure Statement, thus making the GenBank sequences of record in the instant application. Applicants, therefore, respectfully request withdrawal of the Examiner's objection.

New Rejection of Claims Under 35 U.S.C. §112 (first paragraph)

Claims 4-7 and 9-11 stand rejected under 35 U.S.C. §112, first paragraph, as based on a disclosure which is not enabling. According to the Examiner, "the nucleotide sequences of the GenBank accession numbers critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ (CCPA 1976)." Applicants respectfully disagree.

Applicants could not determine the relevance of *In re Mayhew* to the above 35 U.S.C. §112, first paragraph rejection. *In re Mayhew* simply does not teach that "the nucleotide sequences of the GenBank accession numbers critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure." *In re Mayhew* teaches, in general, the circumstances under which 35 U.S.C. §112 first and second paragraph rejections should be applied.

As indicated in the foregoing argument relating to Examiner's New Objection in the specification, Applicants are filing concurrently herewith each of the GenBank sequences described in Table III as part of a PTO-1449 and an Information Disclosure Statement, thus making the GenBank sequences of record in the instant application.

Although most of the GenBank sequences submitted herewith are identical to the GenBank sequences originally made of record at the time of filing of the instant application (as disclosed in Table III), a minority of sequences differ to the originally disclosed ones. Applicants are in the process of obtaining from the National Center for Biotechnology Information (NCBI) the originally disclosed GenBank sequences (as of the time of filing), and will submit them to the Examiner for his review in the near future. According to NCBI's customer service, all GenBank Sequences are dated for the day of publication in GenBank, are archived (including their subsequent amendments, if any), and are publicly

available upon request. The only exception are those sequences which are withdrawn by the submitters because they contain errors.

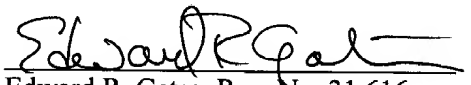
Rejection of Claims Under 35 U.S.C. §112 (second paragraph)

According to the Examiner, claims 4-7 and 9-11 are rejected under 35 U.S.C. §112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner argues that "claims 4-7 and 9-11 are indefinite because they refer to GenBank accession numbers." As previously stated, Applicants are filing concurrently herewith each of the GenBank sequences described in Table III as part of a PTO-1449 and an Information Disclosure Statement, thus making the GenBank sequences of record in the instant application. Applicants believe that with the filing herewith of the PTO-1449 and the subsequent submission by the Applicants of the remaining GenBank sequences (as originally disclosed), the rejection of claims under 35 U.S.C. §112, second paragraph, should be withdrawn.

Applicants believe that each of the pending claims is in condition for allowance. Applicants respectfully request that the Examiner telephone the undersigned attorney in the event that the claims are not found to be in condition for allowance.

If the Examiner has any questions and believes that a telephone conference with Applicants' attorney would prove helpful in expediting the prosecution of this application, the Examiner is urged to call the undersigned at (617) 720-3500 (Extension 232).

Respectfully submitted,



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